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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/960,477	09/24/2001	Yuji Ishihara	2001-1276	6807

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/960,477	ISHIHARA ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-34* is/are pending in the application.

4a) Of the above claim(s) *14-16,19,21-25 and 31-34* is/are withdrawn from consideration.

5)☒ Claim(s) *26-30* is/are allowed.

6)☒ Claim(s) *1-13,17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01-08-04 has been entered.

Claim 18 has been cancelled. Claims 14-16, 19, 21-25, and 31-34 have been withdrawn. Therefore, only claims 1-13, 17, 20, 26-30 are pending.

Claim Rejections - 35 USC § 112—Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-13, 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 17 recites the limitation of "*non-carbamate amine compound*". However, the dependent claims recite compounds actually have a carbamate group. That is, the substituent on Y is an amino group of $-NR^4R^5$ wherein either R^4 and R^5 can be a substituted "*acyl*" group. Thus, the term "*non-carbamate amine compound*" in the independent claims is quite contrary to the limitations in the dependent claims.

Claim Rejections - 35 USC § 112—First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Enablement:** Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 17 recites a "*pharmaceutical composition...which comprises a combination of an α-blocker and a non-carbamate amine compound having acetylcholinesterase-inhibiting action.*" Although the specification cites several α-blockers to be combined with the claimed compounds, such a combination has not been feasible due to a possible adverse effect on the heart and blood pressure. The specification states that α-blockers such as prazosin, or tamsulosin can be combined with a non-carbamate amine compound. However, the specification does not reveal the proportion of an α-blocker and a non-carbamate amine compound. It is a known fact that α-blockers can decrease blood pressure. Thus, without guidance on what proportion of each agent to combine, mixing the two agents could fatally decrease the blood pressure. The state of the art (as evident by the on-line search) does not yield any teaching for such a mixed composition.

Thus, the skilled clinician would have to carry out undue experimentation to formulate such a combination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by **Kawakita et. al.** (US 5,864,039). Even though the claims have been amended to a "*method for improving excretory potency of an urinary bladder...*", such a method reads on the treatment of dysuria which is disclosed on column 3 of US'039. The two compounds on lines 32 and 34 of column 18 (US'039) fall within the scope of the compounds in claims 1-3, and 6-9 with the following substituents:

i. Ar is a phenyl group; n = 6 or 7; R and R' are hydrogen (which makes the portion of Ar-C=O-$(CRR')_n$ of the claims **corresponds** to the portion of "*(6-oxo-6-phenylhexyl)*" or "*(7-oxo-7-phenylheptyl)*" of the disclosed compounds);

ii. Y is a substituted nitrogen-containing heterocyclic group, which **corresponds** to the portion of "*(...**piperidin**-4-yl)methyl)benzamide*".

The 'methyl-benzamide' portion corresponds to the substituent on the instant Y variable. Note, the reference's subgenus of formula (I-4-a) on column 17 gives a clearer structure. In said subgenus, the portion $-(CH_2)_p-B$ corresponds to the instant $Ar-C=O-(CRR')_n$, and the piperidinyl ring corresponds to the instant Y while the 'benzamide' portion corresponds to the substituent on the instant Y.

Note, the preamble "*noncarbamate*" does not seem to exclude substituents having the functional group of –N-C(=O) (i.e., carbamate). Therefore, the teaching of Kawakita et. al. still anticipate the above claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-13, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Goto et. al.** (US 5,527,800) in view of **Tobin et. al.** (Eur. J. Pharm., (1995), Vol. 281, pp. 1-8), and further in view of **Lai et. al.** (Life Sciences, (1998), Vol. 62, No. 13, pp. 1179-1186).

On columns 78 and 79 of US'800, Goto et. al. disclose many peri-fused tricyclic compounds (e.g., compounds #38-40 in Table 63) that fall within the formula recited in the instant claims 1-13, having the following substituents:

iii. Ar is a condensed phenyl, or the peri-fused tricycle of rings (A-C'-(N)-D'), or more specifically, the ring of *pyrrolo[3,2,1-ij]quinolin-4-one*;

iv. Y is piperidinyl substituted with R^6;

v. R^6 is an optionally substituted C_7-aralkyl group.

vi. and n = 2;

In fact the first compound of the instant claim 13 is actually compound #40 of Goto et. al., and the second compound of the instant claim 13 is actually compound #38 of Goto et. al. The disclosed compounds can also inhibit cholinesterase as listed in Table 76 (compounds of Example No. 30-38 and 30-40) on column 230. Although Goto et. al. does not use the disclosed compounds for "*improving excretory potency of urinary bladder*", the teachings of Tobin et. al. and Lai et. al. would provide the nexus to bridge the teaching of Goto et. al. and the instant method claims.

Tobin et. al. confirm that there are three acetylcholine (or muscarinic) receptors namely, M_1, M_2, and M_3. The receptor M_3 mainly causes bladder contraction while M_1 and M_2 modulate the release of acetylcholine (see the second paragraph on the right-hand side column of page 6). Because the M_2 receptor inhibits the release of actylcholine, an anticholingergic compound

would actually activate M_2 receptor. Lai et. al. further reveal that "*activation of M_2 receptor indirectly contributes to bladder contraction...*"

Thus, based on the teachings of Tobin et. al. and Lai et. al., one of the ordinary skill in the art would have been motivated to identify which of the muscarinic receptors Goto's compounds could inhibit and/or activate (as in the case of M_2 receptor), and develop a method of treatment accordingly. Such a task would be within the level of the skilled chemist and/or pharmacologist.

Therefore, at the time of the invention, it would have been obvious to one skilled in the art to apply Goto's compounds in a method for "*improving excretory potency of an urinary bladder*" in view of the combined teachings above.

Allowable Subject Matter

6. Claims 26-30 are allowed. Although the teaching of Goto et. al. disclose the compound as recited in claim 26, said compound has the form of "*amorphous powder*", and not *crystals* as recited herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-T (~10 am ~ 8:30 pm) starting from February 22nd, 2004.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached at 571-272-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting SPE of 1624, at 571-272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

T. Truong
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April 13, 2004

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624